Norovirus Vector-based Vaccine for COVID-19 (coronavirus)

by Anthony of Boston

Norovirus may be an ally of the immune system against respiratory disease. Researchers have not been unable to understand how norovirus can evade immune response by hiding in gut cells. In a test using mice, researchers noticed that in the 1st few days after infection, T cells react strongly and could control the virus, but after 3 days, the T-cells could no longer detect the norovirus. While norovirus remained undetected, T-cell function remained active. I hypothesize that the norovirus regulates the immune system before taking refuge in the gut cells. Noroviruses use two proteins(p48 and p22) to block the host secretory pathway and impede immune responses. The host secretory pathways mediate the intracellular trafficking of proteins, lipids and molecules such as immune mediators like cytokines and chemokines. When viruses are able to subvert the trafficking of the secretory pathway, they are able to enhance their pathogensis. The norovirus virulence factor 1 (VF1) protein antagonizes cytokine induction. This may also serve as a signal for immune cells not to attack the virus. The norovirus minor structural protein VP2 suppresses antigen presentation. Antigen presentation is a key component of adaptive immunity.

The norovirus virulence factor 1 (VF1) protein which antagonizes cytokine induction may serve a hypothesis that the norovirus could reduce both cytokine storm and the pathogenisis of COVID-19. This is an extreme postulate, but even many of the immunosuppresant medications like Janus kinase inhibitors used to reduce cytokine storm have side effects of the same symptomatic manifestations typical of norovirus, which are nausea, vomiting, and diarrhea. However, immunosupressant medications can lower the body's abiity to fight other infections. Norovirus has only been shown to evade immune response, but not inhibit it. In fact, the immune system remains fully functional while the virus hides undetected in gut cells. The norovirus virulence factor 1 (VF1) antagonizes cytokine induction. It is possible that isolating this protein could lead to advanced research

regarding ways to fully inhibit the pathogenesis of COVID-19 as it relates to cytokine storm.

2 major biomarkers in COVID-19 mortality are low platelet count and high mean platelet volume. Platelet count determines the number of platelet in your blood. Platelets are produced in the bonemarrow and released into the bloodstream. These cells circulate within the bloodstream and come together when they spot damaged blood vessels. This act of coming together by the platelets is called clotting. When platelet count is low, less of these cells are available in the bloodstream for clotting. When this happens, a person ability to form clots is reduced. This increases the person's chances of internal bleeding and hemorrhaging issues. When platelet count is high, the more of these cells are present in the blood stream for clotting. The higher this number, the more at risk a person is for developing blood clots.

The mean platelet volume is the size and reactivity of those platelets. A higher mean platelet volume indicates that one's platelets are larger than average. They are also younger as they have been recently released from the bonemarrow. Because of this, it has been found that larger platelets undergo faster activation and are very hyperactive. This raises the risk of blood clots irrespective of the number of platelets. On the other hand, a lower mean platelet volume indicates that the size of the platelet are smaller than average. A lower mean platelet volume also indicates that the platelets are older and less active. This places a person more at risk for a bleeding disorder irrespective of platelet count.

The pathology of COVID-19 often causes the infected to present a low platelet count with a high platelet volume. Both of these factors have been associated with an increased mortality. Since blood clots are more prevalent in those with severe COVID-19, one can more easily infer that high mean platelet volume is the key biomarker, and that low platelet count may simply be the body's attempt at maintaining homeostasis.

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What is interesting about the Norovirus is that its pathology may present an opposite case to COVID-19 when it comes to platelets. A study on rotavirus gastroenteritis which is a stomach virus much like norovirus, but found mostly in young children, found that the mean platelet volume was much lower in children suffering from the rotavirus gastroenteritis compared to those who were not. They also found that platelet count was higher in those infected with the rotavirus. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4359417/

This is exactly the opposite of what is happening in COVID-19. The connection between rotavirus and norovirus is that they are both transmitted via fecal-oral contact, so its likely that they share a similar pathology.

Another interesting note is that the low mean platelet volume found in rotavirus gastroenteritis was associated with inflammatory gastrointestinal diseases, while the high mean platelet volume in COVID-19 was associated with inflammation in the respiratory tract. It would be interesting to see if an increased gastrointestinal inflammation is associated with a decreased respiratory inflammation. If so, a simple virus war can be enacted. Norovirus or rotavirus could be converted into therapeutic agents in the fight against severe COVID-19.

A study entitled "RNA Sequencing of Murine Norovirus-Infected Cells Reveals Transcriptional Alteration of Genes Important to Viral Recognition and Antigen Presentation" found Murine Norovirus to be a potent simulator of the innate immune response. It was found to induce the type 1 interferon response which is responsible for early viral clearance. However, early clearance of viral activity can limit the dynamic of antigen availability and subsequent antibody response needed for the development of more circulating antibodies indicative of strong adaptive immunity. This is essentially what is happening with norovirus infection and makes sense of why the translation of murine norovirus proteins are inhibited. The interferon response attacks the virus in its pre-fusion state, keeping it from releasing its RNA

into the host cell for transcription. (I hypothesize that this pre-fusion viral clearance process manifests as gastrointestinal disturbance—nausea, vomiting, and diarrhea.) As a result, the virus retreats into the gut cells and remains there. Since there was inhibited antigen presentation and antibody production, the virus remained undetected by the immune system. This is problematic for vaccine research for norovirus since norovirus is a virus that triggers the body to inhibit the host cell's transcriptome. The COVID-19 virus does the opposite. It inhibits the interferon response and significantly triggers the cell's transcriptome, releasing its genetic material(RNA) into the host cell for transcription. (I hypothesize that this post-fusion transcriptome manifests as respiratory disturbance—fatigue, cough, and fever.) Thus the body is able to produce a greater amount of neutralizing antibodies via antigen presentation by dendritic cells. At times with COVID-19, the host cell's cellular machinery can be over-triggered and cause an inflammatory response called cytokine storm, which can lead to organ damage. Once again, this is contrary to how the norovirus operates. Norovirus significantly downregulates cytokine receptors. This aspect of activated cell transcriptome in COVID-19 makes it much easier for researchers to develop a vaccine since COVID-19 does not inhibit antigen presentation and antibody production. Thus, the COVID-19 vaccine can simply expose the body to a dead part of the antigen, and trigger the body to produce antibodies in response. The body will thus be protected if exposed to the virus in the future. This is not the case with norovirus since the virus itself inhibits antigen presentation. A norovirus vaccine would have to trigger a mechanism in the body that would immediately inhbit the type I interferon response as soon as the norovirus is presented in the body. It would have nothing to do with antibodies.

Since norovirus and coronavirus are hypothesized to be completely antithetical to each other, a component of each virus can be used as a vector in a vaccine for the other. A component of the norovirus can be used as a vector in a

vaccine for coronavirus. And a component of coronavirus can be used as a vector in a vaccine for norovirus. A viral vector vaccine differs from an mRNA vaccine. In the mRNA vaccines, the part of the antigen is not in the vaccine, but is encoded into the mRNA contained in the vaccine. Once the vaccine is injected into the body, the mRNA enters the cell where its instructions are translated into those proteins which make up the part of the antigen. The immune response then recognizes the proteins as a foreign pathogen and creates antibodies that go to the infected cell, bind to the proteins and mark them for destruction. Once this pathogen is removed, the antibodies remain in the body for a period of time, through which it will recognize and locate any like forms of that specific pathogen it previously destroyed. When the body is later infected by the actual virus, the antibodies will recognize the antigen, bind to the virus and have it removed from the body. This protection lasts for as long as the antibodies for that virus remain elevated in the body.

Viral vector vaccines are similar in that they use the body's own cells to produce the antigen. However instead of mRNA, they use a modified virus to deliver the genetic code of the antigen. The advantage here is that it triggers both the type 1 interferon response, as well as the antibody production response. This would provide protection from infection and also protection after infection.

I want to propose that a COVID-19 vaccine be made using a norovirus vector. A norovirus vector containing the genetic code for COVID-19 antigens should theoretically trigger the body's type 1 interferon response as well as its antibody production via antigen presentation by dendretic cells. In this way, in addition to antibodies, the body is also getting the cytotoxic T-lymphocytes that induce the interferon response. This would protect a person from infection and also provide protection after infection, reducing the risk of serious illness.

I would also propose that a norovirus vaccine be made using a coronavirus vector. A coronavirus vector containing the

genetic code for the norovirus proteins may be able to trigger antigen presentation by inhibiting the interferon response. In this way, the person once exposed to the norovirus may be able to fight off gastrointestinal symptoms with a reduced type 1 interferon response but higher neutralizing antibody response.

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